

## **Remarks**

### **I. Status of the Application and Claims**

At the time that the present Office Action was mailed, the claims pending in the application were 37-56. All of these claims have been cancelled herein and new claims 57-76 have been introduced.

### **II. The Amendments**

The specification of the application has been amended to correct certain errors pointed out in the Office Action.

New claim 57 represents cancelled claim 37 rewritten in a simpler format and amended to more specifically correspond to the process described and exemplified in the application. Independent claim 69 is essentially the reverse reaction of claim 57. The other claims in the application are dependent and are supported by the cancelled claims and by the specification.

The amendments made herein do not add new matter to the application. Entry of the amendments is therefore respectfully requested.

### **III. Objection to the Specification**

On page 2 of the Office Action, the Examiner objects to the specification based upon the allegation that the compound "2',3-dichloroacetophenone" in Example 6 should more properly be named "2,3'-dichloroacetophenone." In addition, the Examiner points out that Example 7 improperly refers to cinnamaldehyde as a ketone. In response, Applicants have introduced amendments that they believe should correct the errors cited by the Examiner.

## **The Rejections**

### **I. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph**

On pages 3-4 of the Office Action, the Examiner argues that claim 37 is indefinite because the phrase "solubility limit" is not properly defined and suggests replacing the phrase with "solubility limit in said solvent system."

In response, Applicants have used essentially the same phrase suggested by the Examiner in the amended claims corresponding to claim 37, *i.e.*, claims 57 and 69. It is respectfully submitted that the Examiner's rejection has therefore been overcome.

Claims 48 and 53 are rejected based upon the allegation that it is unclear whether product is isolated from the organic solvent and the aqueous phase or the product is first partitioned into the organic phase and then isolated from there.

In response, Applicants have amended claims 61 and 64 (roughly corresponding to the rejected claims) to clarify that the product is first separated into the organic phase and then isolated from there. In light of this amendment, Applicants believe that the present rejection has been overcome.

## **II. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph**

On pages 4-11 of the Office Action, all pending claims are rejected based upon the written description and enablement requirements of 35 USC §112, first paragraph. The basic allegation is that the claims are too broad relative to the Examples provided in the application to meet either the written description or enablement requirements.

In response, claims have been amended in a manner that Applicants believe should put them into a form that the Examiner finds more acceptable with respect to the written description and enablement requirements of patentability. In particular, Applicants submit that the amended claims do, in fact, recite specific structural characteristics of products and reactants (*e.g.*, “carbonyl compounds” and “alcohols,” claims 57 and 69; “aldehyde” and “unsymmetric ketone,” claims 58 and 70; an “acetophenone optionally substituted with one or more halogens,” claims 65, and 68; specific acetophenones, claim 66; and “cinnamaldehyde,” claims 67 and 68). Claims also require specific cofactors (NADH or NADPH) and particular enzymes (dehydrogenases that use these cofactors). In light of these amendments, Applicants believe that there is now, in fact, a clear nexus between the methods recited and the products made and that compounds are not simply described in functional terms. The amended claims do not include all redox reactions and do not, in Applicants’ opinion, extend beyond what one of skill in the art would be able to perform based upon the disclosure. Therefore, Applicants believe that the written description and enablement

requirements have been met and respectfully request that the Examiner reconsider and withdraw the present rejection.

## II. Rejection of Claims Under 35 U.S.C. § 103

On pages 11-15 of the Office Action, claims are rejected as being obvious in light of Bomannus (US 2003/0054520), and Yamamoto (US 2002/0064847), Sjoberg (US 6,500,661), Orlich (*Biotechnol. Bioeng.* 65:357-362 (1999) or Gröger (*Org. Lett.* 5:173-176 (2003)). The Examiner alleges that the references teach a coupled reaction involving the oxidation or reduction of a substrate and the use of NAD(P)/NAD(P)H as a cofactor. The Bomannus, Yamamoto, Sjoberg, and Orlich references allegedly teach reactions in which ketones, aldehydes and alcohols are used in an enzymatic system along with regenerating cofactors. Gröger is cited as teaching the production of alcohols from ketones using essentially the same components as those claimed.

Applicants respectfully traverse this rejection.

The primary thing that distinguishes the reaction system claimed by Applicants from the prior art is the use of an aqueous solvent system in which poorly soluble compounds are at a concentration above their solubility limit, thereby creating an emulsion or suspension. The Examiner appears to recognize that the references cited do not describe this but alleges that Gröger makes such a system obvious because it recognizes that: a) higher concentrations of reactants increase production; and b) enzyme activity is higher in an aqueous system. Applicants respectfully disagree.

As can be seen in scheme 2 of Gröger and the immediately following text, this reference teaches a reaction that is carried out in a two phase system in which substrates are primarily located in an organic phase and enzymes are primarily located in an aqueous phase. There are no teachings that suggest that the solubility limit of the ketones is exceeded in either phase or that an emulsion or suspension forms. In fact, it is apparent that the reason for using a biphasic system is to avoid mixing ketones with the other reaction components at a concentration where the ketones would not be soluble. Using a single phase aqueous system in which ketones are at a concentration at which they form an emulsion (*i.e.*, using the system required by Applicants' claims) is therefore incompatible with the rationale on which the

Gröger reference is based and, as such, is nonobvious in light of the teachings of this reference.

One reason that the Gröger scientists may not have wanted to exceed the solubility limit of the aqueous system is that, when an emulsion is formed, ketones clump together to form hydrophobic droplets that can contact and denature enzymes in the same manner as an organic solvent. For this reason, concentrations of ketone high enough to cause emulsions would be expected to decrease enzymatic activity and lead to decreased overall yield. This expectation is entirely consistent with the teachings of Gröger and means that one of skill in the art could not have a reasonable expectation of success in using Applicant's claimed process.<sup>1</sup> Moreover, Applicants demonstrated that the expectation that emulsions of ketones will rapidly inactivate enzymes is correct (see Example 2 of the application and Figure 2). What is surprising is that, despite an almost complete loss of activity over a period of 5 hours, alcohol yields remain high (see Examples 3-7 and the corresponding figures). The unexpected nature of this discovery is described in the application on page 5, line 23 - page 6, line 5, which reads:

In contrast to the opinion which can be deduced from the prior art, in particular in view of the feared dramatic decreases in the activity of the enzymes and here in particular in that of the formate dehydrogenase from *Candida boidinii* in the presence of organic components with a logP value of <3.5 (under which also most of the substrates and products fall), it is possible, surprisingly and in spite of the direct presence of such organic components (substrates/ products), to operate the coupled enzymatic reaction system without a significant loss in activity (of one) of the enzymes. Comparison example 2 underlines this surprising effect; according to this drastic decrease in activity observed in comparison example 2, with a virtually complete loss in activity of the FDH within only a few hours, it would have been expected that no significant conversions result under the reaction conditions according to the invention.

In light of the above considerations, Applicants respectfully submit that the claims now pending meet the nonobviousness requirement of patentability.

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<sup>1</sup> An obviousness determination requires not only a motivation to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via the combination (*Medichem v. Rosado*, 437 F.3d 1157 (Fed. Cir. 2006)).

### Conclusion

In light of the considerations above, Applicants submit that all of the Examiner's rejections have been overcome. It is therefore requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (240)683-6165.

Respectfully submitted,

LAW OFFICE OF MICHAEL A. SANZO, LLC

By: 

Michael A. Sanzo  
Reg. No. 36,912  
Attorney for Applicants

Date: December 9, 2008  
15400 Calhoun Drive, Suite 125  
Rockville, Md. 20855  
(240)683-6165